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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,678	09/21/2006	Jerome Berger	1485-000016/US/NP	5636

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,678	BERGER ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-10 and 22* is/are pending in the application.

4a) Of the above claim(s) *1-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-10 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 4/22/2009 were entered.

Response to Arguments

2. Applicants' arguments, filed 4/22/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Priority

3. The earliest effective filing date afforded the instantly claimed invention has been determined to be 3/22/2004, the filing date of PCT/EP04/02988 of which this Application is a U.S. National Stage Application submitted under 35 U.S.C. 371.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. **Claims 8-10 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Domard et al* (cited in a previous Action), as evidenced by *Industrial Research Ltd Catalog* (cited in a previous Action) and *Granja et al* (cited in a previous Action), and in view of *Baumann et al* (cited in a previous Action) and *Nettles et al* (cited in a previous Action).**

6. Instant claim 10, as amended, is drawn to a homogenously reacetylated chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 30-60% obtained by a process (said process being recited by the claim) for use in the preparation of a pseudo-thermosetting neutralized chitosan composition forming a phosphate-free transparent hydrogel at a temperature higher than 5° C.

7. Concerning the process for obtaining the homogenously reacetylated chitosan as recited by instant claim 10, as discussed in the previous Action mailed on 1/22/2009, product-by-process claims are not limited to the manipulations of the recited steps, if the product in the product-by--process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process (See MPEP 2113). In the instant case, the product in the product-by-process claim 10 is a homogenously reacetylated chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 30-60% (which also reads on new claim 22). And, as discussed in the previous Action, *Domard et al* teach chitosan (obtained from squid endoskeletons, purified by dissolving, filtering, precipitating, washing and freeze-drying) (Paragraph 0033) which is **re-acetylated** with acetic

anhydride in a hydro-alcoholic medium to obtain a **degree of chitosan acetylation of 50%** (Paragraph 0040). As such, *Domard et al* explicitly teach reacetylated chitosan having a ***deacetylation*** degree of 50% (which encompasses 30-60% as recited by instant claim 10). However, *Domard et al* do not disclose **(A)** whether the chitosan is homogenously reacetylated or **(B)** whether the chitosan has a molecular weight of not smaller than 200 kDa.

8. **As to (A)**: *Domard et al* do not explicitly disclose homogenously reacetylated chitosan (as recited by instant claim 10). Yet, as stated by Applicant, "in addition to the proportion of acetylated and deacetylated monomers of chitosan represented by its degree of deacetylation, the homogenous distribution mode of these monomers is an ***essential*** criteria to get transparent and phosphate-free hydrogels" (Instant Specification Page 8, Lines 16-19, emphasis added). Notably, *Domard et al* specifically teach the formation of hydrogels from the re-acetylated chitosan have a deacetylation degree of 30-60% (specifically, 50%) without the addition of phosphate (Paragraphs 0042-0043). That is, *Domard et al* teach the formation of phosphate-free hydrogels. Thus, it is asserted that the reacetylated chitosan taught by *Domard et al* must, by necessity, be homogenously reacetylated since homogenous reacetylation is an essential criterion to the formation of phosphate-free hydrogels. See *In re Fitzgerald* 205 USPQ 594, 597, 619 F2d 67 (CCPA 1980): the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on." Furthermore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to reacetylate the chitosan specifically using homogenous conditions as evidenced by *Baumann et al* which explicitly state that "reactions are to be carried out in homogeneous media, resulting in a statistical distribution of functional groups along the polymer chain. In contrast, heterogeneous

reactions are known to result in block structures that cause solubility problems" (Page 44, Column 2). Thus, while it is asserted that the reacetylated chitosan taught by *Domard et al* must, by necessity, be homogenously reacetylated, even *assuming arguendo* that the chitosan is not homogenously reacetylated, the skilled artisan would have been motivated to reacetylate the chitosan under homogeneous conditions in an effort to avoid solubility problems associated with heterogeneous reacetylation of chitosan in view of *Domard et al.*

9. Applicants argue that "Bauman teaches away from a homogenously reacetylated chitosan having a molecular weight of not smaller than 200 kDa and deacetylation degree of 30-60%" (Applicant Argument, Pages 14-15). Since *Bauman et al* do not criticize, discredit, or otherwise discourage a homogenously reacetylated chitosan having a molecular weight of not smaller than 200 kDa and deacetylation degree of 30-60%, they do not "teach away" as asserted by Applicants. In re Fulton, 391 F.3d 1195 (Fed. Cir. 2004). Moreover, however, *Bauman et al* (which Applicants acknowledge mention that most reactions are to be carried out in homogenous media for avoiding solubility problems (Applicant Argument, page 15)) provide motivation to the skilled artisan to homogenously reacetylate the chitosan disclosed by *Domard et al.* Applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. Although Applicants contend that Bauman et al "do not provide any hint as to whether this general statement applies to reacetylation reactions in particular... nor provide any guidance for performing a homogenous reacetylation according to claim 10, nor any teaching about the physical properties of N-acetylated chitosan" (Applicant Argument, Page 15), it is believed the clear teaching would motivate one of ordinary skill in the art to homogenously reacetylate chitosan in an effort to

avoid solubility problems associated with heterogeneous reacetylation of chitosan in view of *Domard et al.*

10. **As to (B)**: *Domard et al* also do not disclose the molecular weight of the taught chitosan. However, as evidenced by the *Industrial Research Ltd Catalog* for Squid pen derived chitin and chitosan, "Squid pens contain β-chitin… therefore, squid pen derived β-chitin is expected to have a higher molecular weight than crab or shrimp derived chitin. The chitosan preparted by deacetylating squid chitin is also expected to have a higher molecular weight than chitosan derived from other sources" (available online at http://www.irl.cri.nz/productsandservices/products-fine-chemicals/Squidpenderivedchitinandchitosan.aspx). Applicant argues that the *Industrial Research Ltd Catalog* may not constitute prior art. However, the *Industrial Research Ltd Catalog* is not being applied as prior art, but merely as evidence to support the assertion that the chitosan in the teaching of *Domard et al* would necessarily be more than 200 kDa. Accordingly, Applicants' argument is not found persuasive. Furthermore, as evidenced by *Granja et al* (who teach injectable chitosa-hydroxyapatite microspheres for the promotion of localized bone regeneration (Abstract)) squid chitosan presented a viscosity average molecular weight of 2480 kDa (Page 573). Accordingly, although *Domard et al* do not explicitly disclose the molecular weight of the homogenously reacetylated chitosan, it is asserted that the homogenously reacetylated chitosan taught would have a molecular weight of not smaller than 200 kDa as recited by instant claim 10 based on the *Industrial Research Ltd Catalog* and on *Granja et al*. "Where… the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to

prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product" *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433, 562 F2d 1252 (CCPA 1977). See also *In re Fitzgerald* 205 USPQ 594, 597, 619 F2d 67 (CCPA 1980): the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on." In the instant case, the chitosan taught by *Domard et al* is substantially similar to the instantly claimed chitosan and is produced by a substantially similar process. Accordingly, absent evidence to the contrary, it is asserted that the chitosan taught by *Domard et al* would have a molecular weight of not smaller than 200 kDa.

11. Alternatively, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to provide chitosan having a molecular weight of not smaller than 200 kDa. As stated by MPEP 2144.05:

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)

. In the instant case, the molecular weight of chitosan is clearly a result-effective variable. As disclosed by *Domard et al*, the invention concerns the preparation of cartilaginous neo-tissue that is capable of being grafted (Abstract). As taught by *Nettles et al*, "properties of porous chitosan matrices such as microstructure, crystallinity, and mechanical strength can be varied by altering chitosan concentration, freezing rate, and the molecular weight and percent deacetylation of the starting

material… Thus there are many ways to control and optimize the physical characteristics of chitosan scaffolds" (Page 1010, Column 1). Thus, the skilled artisan would have been motivated to optimize the molecular weight of the chitosan to provide scaffolds useable in the invention taught by *Domard et al* having the most desirable properties. In view of the disclosure of *Nettles et al*, a person of ordinary skill in the art would have reasonably predicted that altering the molecular weight of the chitosan would accomplish this.

12. Accordingly, the prior art teach the homogenously reacetylated chitosan as recited by the product-by-process of instant claim 10. Concerning the recitation in claim 10 that the claimed homogenously reacetylated chitosan is "for use in the preparation of a pseudo-thermosetting neutralized chitosan composition forming a phosphate-free transparent hydrogel", as discussed in the previous Action mailed on 1/22/2009, use limitations within product claims do not carry patentable weight unless the recitation of the intended use of the claimed invention results in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In the instant case, the chitosan taught by *Domard et al* would be capable of being used in the preparation of a pseudo-thermosetting neutralized chitosan composition forming a phosphate-free transparent hydrogel at a temperature higher than 5°C as claimed. Specifically, *Domard et al* teach that the reacetylated chitosan is "then poured into a receptacle that provided a large free surface/volume ratio and was then placed in an oven at 45°C for the time required for the gel to set" (Paragraph 0042) and "[t]o obtain a hydrogel which was not soluble in water at pHs of the order of 6 or 7, the hydrogel obtained was neutralized by placing it for about one hour in a basic medium, for example 0.1

molar sodium hydroxide" (Paragraph 0043). Accordingly, *Domard et al* teach the formation of a phosphate-free hydrogel at a temperature higher than 5°C. Furthermore, it is asserted that, absent evidence to the contrary, the hydrogel would be transparent. "Where… the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product" *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433, 562 F2d 1252 (CCPA 1977). See also *In re Fitzgerald* 205 USPQ 594, 597, 619 F2d 67 (CCPA 1980): the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on." In the instant case, the reacetylated chitosan taught by *Domard et al* in view of *Baumann et al* is substantially similar to the instantly claimed chitosan and is produced by a substantially similar process; furthermore, the hydrogel is substantially similar and produced by substantially the same process. Accordingly, absent evidence to the contrary, it is asserted that the resulting hydrogel taught by *Domard et al* in viewo of *Baumann et al* would be transparent.

13. Applicants traverse on a variety of grounds. Although Applicants' arguments are not altogether clear, it is believed that the following represent the entirety of Applicants' remaining arguments:

14. **(1)** Applicants argue that *Domard et al* do not teach *formation* of the recited product by the same *process* as recited by instant claim 10. Specifically, Applicants contend that "Domard does not teach a ***process*** of homogenously reacetylating a chitosan from a chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 80 to 90%" (Applicant Argument, Page 9, emphasis added; see also Applicant Argument, Pages 10-12: "one

skilled in the art would not have any guidance to... use of a chitosan with acetylation degree of <10%"; "one skilled in the art would not have any guidance to choose the molecular weight of the chitosan for subjecting to reacetylation"; Domard "does not teach a process of homogenously reacetylating a chitosan from a chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 80 to 90%", "Domard teaches a reacetylation process of chitosan in the presence of 1,2 propanediol, whereas the reacetylation process according to the invention does not use 1,2 propanediol"). Yet, as previously discussed, product-by-process claims are not limited to the manipulations of the recited steps, if the **product** in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process (See MPEP 2113). For all of the reasons discussed above, the product in the instant product-by-process claim is taught by the prior art. Accordingly, the instantly recited process limitations are not afforded patentable weight. Thus, Applicants' arguments that *Domard et al* do not teach *formation* of the recited product by the same *process* as recited by instant claim 10 is not found persuasive.

15. **(2)** Applicants additionally argue that *Domard et al* do not teach the recited *use* of the product (i.e., in the preparation of a pseudo-thermosetting neutralized chitosan composition forming a phosphate-free transparent hydrogel) (Applicant Argument, Page 9). Yet, as previously discussed, use limitations within product claims do not carry patentable weight unless the recitation of the intended use of the claimed invention results in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Applicants argue that "a homogenously reacetylated chitosan with a deacetylation degree higher than 60% would ***not*** form a pseudo-thermosetting neutralized

chitosan composition forming a phosphate-free transparent hydrogel" (Applicant Argument, Pages 9-10). That is, Applicants argue that the prior art structure would not be capable of performing the intended use. However, the prior art structure does not comprise a deacetylation degree higher than 60%. Rather, *Domard et al* teach chitosan (obtained from squid endoskeletons, purified by dissolving, filtering, precipitating, washing and freeze-drying) (Paragraph 0033) which is re-acetylated with acetic anhydride in a hydro-alcoholic medium to obtain a **degree of chitosan acetylation of 50%** (Paragraph 0040) (i.e., a degree of deacetylation of 50%, and which is ***not*** higher than 60%) and which can be used to form a hydrogel (Paragraphs 0042-0044). Applicants' arguments that the prior art product would not have "pseudo-thermosetting properties" and "would not intrinsically have the properties of the claimed product" (Applicant Argument, Page 10) are not the kind of factual evidence required to rebut a *prima facie* case of obviousness, and such statements which are not evidence should be supported by an appropriate affidavit or declaration.

16. **(3)** Applicants also argue that the prior art do not teach chitosan ***having a molecular weight of not smaller than 200 kDa***. Yet, for the reasons discussed above, it is asserted that the chitosan obtained from squid endoskeletans used in the teaching of *Domard et al* would necessarily have a molecular weight of not smaller than 200 kDa absent evidence to the contrary. Since Applicants have introduced no evidence to suggest otherwise, Applicants' arguments are not considered persuasive. However, even *assuming arguendo* that the chitosan obtained from squid endoskeletans used in the teaching of *Domard et al* is less than 200 kDa, it is clear from the above prior art that molecular weight of chitosan is a result-effective variable which the skilled artisan would have been motivated to optimize.

17. Accordingly, for all of the foregoing reasons, Applicants' arguments are not found persuasive. As such, the rejection of claim 10 is maintained. And new claim 22 is rejected.

18. Instant claims 8-9 have been amended to depend from instant claim 10, and further define the process by with the product of instant claim 10 is prepared. For the same reason as applied to instant claim 10, claims 8-9 are rejected. That is, as discussed above, if the product in the product-by--process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process (See MPEP 2113). Since the product in the product-by-process claims 8-9 is the same as that recited by instant claim 10, the claims are hereby rejected.

Conclusion

The new ground(s) of rejection presented in this Office action are necessitated by Applicants' amendments to the claims. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
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